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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/731,073	SINGH ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,14,15 and 18-22* is/are pending in the application.

4a) Of the above claim(s) *14,15 and 18-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 12, 13, 16 and 17 have been canceled. Claims 1-11, 14, 15 and 18-22 remain pending.

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-11, in the reply filed on 7-3-06 is acknowledged.

Claims 14, 15 and 18-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 7-3-06.

Specification

The status of the application on pg 1, line 1, needs updated to indicate the parent case has been abandoned.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. The nucleic acid sequences in Table II (pg 16) having 10 or more nucleotides require SEQ ID NOs. Applicants must file a "Sequence Listing" accompanied by directions to enter the listing into the specification as an amendment. Applicant also must provide statements regarding sameness and new matter with regards to the CRF and the "Sequence Listing." Failure to fully comply with the sequence rules in response to the instant office action will be considered non-responsive.

The abstract of the disclosure is objected to because it is too long. Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 1 requires making a transgenic avian lacking expression of an endogenous immunoglobulin comprising inactivating at least one endogenous heavy chain immunoglobulin locus in at least one avian cell; generating at least one avian from said at least one avian cell; and optionally breeding said at least one avian to obtain a transgenic avian lacking expression of endogenous immunoglobulins. Claims 2-10 requires introducing at least one exogenous immunoglobulin locus into at least one avian cell.

Transgenics are defined as organisms in which new DNA has been introduced into the germ cells by injection into the nucleus of the ovum (Stedman's Medical Dictionary, see attached definition).

The specification suggested inactivating the heavy chain immunoglobulin gene in birds using various methods known in the art, e.g. Jakobovits (US Patent 5,998,209, 12-7-99), Ginsburg (US Patent 6,006,778, 5-23-00) or Kucherlapati (US Patent 5,939,598, 8-17-99) (pg 25, line 9; pg 39, line 18-26; pg 54, lines 1-10). The references cited and the art at the time of filing taught transfecting mouse ES cells with a knockout construct, culturing the cells over a period of time, selecting the ES cells having the desired knockout and implanting the ES cells into a recipient embryo. See, for example, Kucherlapati who taught selection of mouse ES cells having the desired knockout was required to make a mouse having an immunoglobulin gene knockout (col. 10, line 47). The art at the time of filing did not teach how to inactivate a gene in an avian ES cell or how to culture a transfected avian ES cell over a period of time such that a transgenic avian was made.

Throughout the specification, the specification suggests introducing the exogenous genes using methods known in the art, both in avians and mice. For example, Stage XI PGCs had been isolated from chickens, transduced with retrovirus, and immediately injected into the vasculature of Stage 15 chick embryos to obtain germline transmission of a transgene (Vick, Proc. R. Soc. Lond., 1993, Vol. 251, pg 179-182). Plasmid DNA had been injected into the germinal disc of chick zygotes isolated before being laid to obtain germline transmission of a transgene (Love, Bio/Technology, 1994, Vol. 12, pg 60-63). Retroviral vectors had been injected into the subgerminal cavity of an avian embryo in a freshly laid egg to obtain germline transmission of a transgene (Thoroval, Transgenic Research, 1995, Vol. 4, pg 369-376).

Retroviral vectors had been used to introduce a truncated antibody receptor into chickens "somatically" and express the receptor in the bursa at hatch (Sayegh, Dec. 15, 1999, Vol. 72, pg 31-37; pg 32, 2nd full para., lines 2-5 and 16-18; para. bridging pg 33-34).

Pain (1996, Development, Vol. 122, pg 2339-2348) taught culturing chicken ES cells over a period of time, but did not teach transfecting the ES cells and maintaining the ES cells over that period of time.

Mohammed (1998, Immunotechnology, Vol. 4, pg 115-125) taught that although using hens for the production of recombinant human antibodies (rhAb) has been discussed, it has never been demonstrated. Mohammed transfected a lymphoblastoid cell line with a retrovirus encoding a rhAb, injected the cells into a chicken and obtained expression of the rhAb in the egg yolk and sometimes the egg white (pg 116, col. 1, 2nd ¶; col. 2, 1st full ¶). Mohammed suggested suppressing the expression of endogenous chicken Ig but did not teach how to inactivate a gene in an avian (pg 124, col. 2, 2nd ¶, line 9) and did not teach how to obtain a transgenic avian having an inactivated immunoglobulin gene. The transfected lymphoblastoid cell line (DT40) maintained in culture for two days used by Mohammed to obtain antibodies in the egg cannot be used to disrupt chicken heavy chain immunoglobulin gene in a knockout chicken because the transfected chicken DT40 cells are differentiated cells that cannot be used to make a knockout chicken. The method of Mohammed is not a method of disrupting a chicken gene in a transgenic chicken because the transfected cells cannot integrate into the germline of a chicken, which is essential to make a knockout chicken.

Fukagawa (Nucleic Acids Res. 1999, Vol. 27. pg 1966-1969) taught making a "knockout" construct that disrupted the chicken HPRT gene in DT40 cells that required Cre recombinase (¶ bridging pg 1966-1967).

Since the time of filing, Ishida (2002, Cloning Stem Cells, Vol. 4, pg 91-102) suggested making chickens expressing human antibodies but did not teach how to make transgenic chickens or how to inactivate chicken genes (see abstract).

Ivarie (Trends in Biotechnology, Jan. 2003, Vol. 21, pg 14-19) taught that because of the complex process by which a bird makes and lays eggs, transgenic procedures for birds have lagged far behind those of other organisms. Ivarie cites Pain who taught long-term culture of non-transfected, blastodermal cells that provided germline transmission; however, no transgenic birds have been made using transfected ES cells or PGCs. The biggest obstacle to overcome in making transgenic birds using transfected ES cells or PGCs is the loss of germline competence during culture of transfected ES cells and PGCs (pg 14, col. 2, 3rd full ¶, 1st sentence; pg 17, col. 1, 2nd full ¶, last two sentences; pg 17, sentence bridging col. 1-2; pg 17, col. 2, last sentence).

Thus, the state of the art at the time of filing was that "knockout" constructs had not been stably transfected into chicken ES cells or PGCs such that "knockout" chickens having a disruption in a chicken gene had been obtained because the transfected chicken ES cells or PGCs could not be cultured over an adequate period of time while maintaining the ES cell or PGC phenotype and integrating the "knockout" construct.

The specification suggested culturing avian ES cells using the method of Pain after transfection for 10-14 days (pg 58, lines 1-16)). However, Ivarie (cited above) taught since the time of filing that because of the complex process by which a bird makes and lays eggs, transgenic procedures for birds have lagged far behind those of other organisms. Ivarie cites Pain who taught long-term culture of non-transfected, blastodermal cells that provided germline transmission; however, no transgenic birds have been made using transfected ES cells or PGCs. The biggest obstacle to overcome in making transgenic birds using transfected ES cells or PGCs is the loss of germline competence during culture of transfected ES cells and PGCs (pg 14, col. 2, 3rd full para., 1st sentence; pg 17, col. 1, 2nd full para., last two sentences; pg 17, sentence bridging col. 1-2; pg 17, col. 2, last sentence).

The specification suggests transferring DNA into CES cells by ES (pg 60, lines 13-20). This too requires stably transfecting cells that carry the transgene while maintaining the ES cell phenotype which had not been done according to Ivarie (cited above) and has not been enabled by applicants. The specification provides no means of doing so beyond what was known in the art. Ivarie specifically described methods of culturing ES cells known in the art as being inadequate to obtain a transgenic avian having an inactivated gene.

Overall, the specification does not overcome the unpredictability in the art so that one of skill could culture transfected avian ES cells or PGCs and select cells having the desired knockout and obtain germline chimeras having an inactivated gene as claimed. The specification provides no other means of isolating ES cells or PGCs, transfecting

the cells or culturing the transfected cells such that the desired cells could be selected. Without such guidance, it would require one of skill undue experimentation to obtain a transgenic avian having an inactivated gene as claimed.

Accordingly, applicants have not enabled those of skill to inactivate an immunoglobulin gene in an avian cell, generate an avian from the cell and breed the avian to obtain offspring that lack expression of the immunoglobulin gene as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3 and 5-10 are indefinite because of the term "locus." The term does not make sense in context of the claims because a "locus" is the position of gene in a chromosome and not a nucleic acid sequence that can be inactivated as claimed.

Claim 1 lacks a nexus between the endogenous heavy chain in the "inactivating" step and the resulting transgenic avian endogenous immunoglobulins in the "optionally breeding" step.

Claim 1 does not make sense because without the "optionally breeding" step, no transgenic avian is produced. The breeding step is not optional.

Claim 2 is indefinite because it is unclear if the "at least one avian cell" is the avian cell of claim 1 or a different cell. If the cell in claim 2 is the cell in claim 1, the distinction should be clearly set forth.

Claims 2, 3, 5 and 7-10 are indefinite because the limitation of "exogenous" is indefinite. It cannot be determined whether the antibody or locus is "exogenous" to all avians, a type of avian, or one particular avian because the term "exogenous" is a relative term.

Claim 3 is indefinite it does not clearly set forth the limitation by stating the immunoglobulin is a heavy chain constant region.

Claim 5 is indefinite because "at least a portion of the V_H, D_H, J_H and C_H regions" is unclear. It is unclear if a portion of each region is required or a portion of at least one of the regions is required.

Claim 5 is indefinite because the phrase "the V_L, J_L, and C_L regions" in parent claim 3 lacks antecedent basis.

Claim 6 is indefinite because it is unclear if the "at least one avian cell" is the avian cell of claim 1 or a different cell. If the cell in claim 6 is the cell in claim 1, the distinction should be clearly set forth.

Claim 7 is indefinite because it is unclear if the "at least one avian cell" is the avian cell of claim 6 or a different cell. If the cell in claim 7 is the cell in claim 6, the distinction should be clearly set forth.

Claim 8 is indefinite it does not clearly set forth the limitation by stating the immunoglobulin light chain of claim 7 is a human light chain.

Claim 9 is indefinite it does not clearly set forth the limitation by stating the immunoglobulin light chain of claim 7 is a human light chain constant region.

Claim 9 is indefinite because "at least a portion of the V_L, J_L and C_L regions" is unclear. It is unclear if a portion of each region is required or a portion of at least one of the regions is required.

Claim 9 is indefinite because "the V_L, J_L and C_L regions" lack antecedent basis in claim 7.

Claim 10 is indefinite because it limits the type of avian cell without limiting the type of avian produced. A turkey cell, for example, does not have a nexus with producing any transgenic avian as broadly claimed.

The claims appear to be free of the prior art.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER